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Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial

Pallavi Mandal, James D Chalmers, Catriona Graham, Catherine Harley, Manjit K Sidhu, Catherine Doherty, John W Govan, Tariq Sethi, Donald J Davidson, Adriano G Rossi, Adam T Hill



Summary

Background Bronchiectasis is characterised by chronic cough, sputum production, and recurrent chest infections. Pathogenesis is poorly understood, but excess neutrophilic airway inflammation is seen. Accumulating evidence suggests that statins have pleiotropic effects; therefore, these drugs could be a potential anti-inflammatory treatment for patients with bronchiectasis. We did a proof-of-concept randomised controlled trial to establish if atorvastatin could reduce cough in patients with bronchiectasis.

Methods Patients aged 18–79 years were recruited from a secondary-care clinic in Edinburgh, UK. Participants had clinically significant bronchiectasis (ie, cough and sputum production when clinically stable) confirmed by chest CT and two or more chest infections in the preceding year. Individuals were randomly allocated to receive either high-dose atorvastatin (80 mg) or a placebo, given orally once a day for 6 months. Sequence generation was done with a block randomisation of four. Random allocation was masked to study investigators and patients. The primary endpoint was reduction in cough from baseline to 6 months, measured by the Leicester Cough Questionnaire (LCQ) score, with a lower score indicating a more severe cough (minimum clinically important difference, 1·3 units). Analysis was done by intention-to-treat. The trial is registered with ClinicalTrials.gov, number NCT01299181.

Findings Between June 23, 2011, and Jan 30, 2011, 82 patients were screened for inclusion in the study and 22 were excluded before randomisation. 30 individuals were assigned atorvastatin and 30 were allocated placebo. The change from baseline to 6 months in LCQ score differed between groups, with a mean change of 1·5 units in patients allocated atorvastatin versus –0·7 units in those assigned placebo (mean difference 2·2, 95% CI 0·5–3·9; $p=0\cdot01$). 12 (40%) of 30 patients in the atorvastatin group improved by 1·3 units or more on the LCQ compared with five (17%) of 30 in the placebo group (difference 23%, 95% CI 1–45; $p=0\cdot04$). Ten (33%) patients assigned atorvastatin had an adverse event versus three (10%) allocated placebo (difference 23%, 95% CI 3–43; $p=0\cdot02$). No serious adverse events were recorded.

Interpretation 6 months of atorvastatin improved cough on a quality-of-life scale in patients with bronchiectasis. Multicentre studies are now needed to assess whether long-term statin treatment can reduce exacerbations.

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Introduction

Bronchiectasis is a chronic disabling respiratory disorder characterised by cough, sputum production, and recurrent chest infections. It is regarded as an orphan disease, not because of its rarity but because of the paucity of randomised trial data: 133 trials were identified for bronchiectasis in a recent PubMed search, versus 8748 for asthma.¹ The true incidence of bronchiectasis in the modern era of chest CT is not known. At our institution in Edinburgh, UK, we provide secondary care for more than 750 patients with bronchiectasis, from a total population of about 490 000. Patients frequently use primary-care and secondary-care resources through consultations, attendance at accident and emergency units, and admissions.

The pathogenesis of bronchiectasis is poorly understood, but pulmonary pathological findings show excess neutrophilic airway inflammation. However, more than two-thirds of patients are infected chronically with

potential pathogenic organisms.² The amplified level of neutrophilic airway inflammation leads to damage of the bronchial wall, paradoxically promoting more airways inflammation and bacterial infection, and a vicious cycle is seen.³ Markers of systemic inflammation—eg, C-reactive protein—are raised in patients with bronchiectasis and correlate directly with disease severity and inversely with lung function and quality of life in stable-state bronchiectasis.⁴ Long-term evidence-based treatments for the disorder are scarce; chest physiotherapy and continued use of antibiotics are current therapeutic approaches. Concerns have been raised about use of long-term antibiotics because of resistance, side-effects, and health-care-associated infections. In view of these concerns, and the excess inflammatory response in the airways, investigation is underway into the efficacy of anti-inflammatory treatments.

Statins have pleiotropic effects, including modulation of the innate and adaptive immune systems and

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reduction of inflammation.^{5,6} For example, statins attenuate neutrophil recruitment in animal and human experimental systems of sterile inflammation.^{7,8} In murine models of pulmonary infection with *Staphylococcus aureus*, high-dose statin treatment enhanced the formation of extracellular DNA traps by phagocytes within the lung and protected against dissemination of infection.^{9,10} Boyd and colleagues¹¹ reported that prolonged high-dose simvastatin had a strong dose-dependent effect on protection against *Streptococcus pneumoniae* in a mouse model of lung infection, indicated by reduced neutrophil infiltration, maintenance of vascular integrity, and diminished chemokine production. Furthermore, findings of observational studies in individuals with community-acquired pneumonia showed a reduction of 30-day mortality in patients who were also receiving statins.¹²

We postulated that long-term statin treatment would improve symptoms in patients with bronchiectasis by reducing neutrophilic airway inflammation. The aim of our proof-of-concept study was to establish if atorvastatin could reduce cough, a key feature in patients with bronchiectasis. We chose atorvastatin because it is a potent statin for reduction of cholesterol and has a low side-effect profile, and we administered the drug at the maximum dose because our study was proof-of-concept and use of the maximum dose avoids the need to repeat the study at different doses.

Methods

Study population

We recruited patients aged 18–79 years with clinically significant bronchiectasis who were receiving treatment at the South East of Scotland Bronchiectasis Clinic, based at the Royal Infirmary, Edinburgh, UK. Inclusion criteria were cough and sputum production when clinically stable; two or more chest infections in the preceding year; and bronchiectasis confirmed on chest CT. For diagnosis on CT, bronchial dilatation had to be present (bronchus:arterial ratio >1).

We excluded current smokers or former smokers who had stopped smoking less than 1 year previously, those with a greater than 15 pack-year history, or those with predominant emphysema on CT scan; people with cystic fibrosis; individuals with active allergic bronchopulmonary aspergillosis; patients with active tuberculosis; people with poorly controlled asthma; women who were pregnant or breastfeeding; individuals with a known allergy to statins; those currently on statins or who had used them within the previous year; people with active malignant disease; individuals with chronic liver disease; and patients on long-term oral macrolides (because of the known interaction with statins). We also excluded people who had chronic colonisation with *Pseudomonas aeruginosa* (defined as two or more isolates of *P aeruginosa* while clinically stable in the 6 months before the study), because these individuals have more

severe disease^{13,14} and the objective of our study was to investigate the effects of atorvastatin in patients with less severe bronchiectasis.

We obtained ethics approval from the South East of Scotland research ethics committee. All patients gave written informed consent.

Randomisation and masking

We randomly allocated patients to receive either high-dose atorvastatin (80 mg) or a placebo (lactose), given orally once a day for 6 months. The placebo was not matched to atorvastatin in appearance. Tayside Pharmaceuticals (NHS Tayside, UK) generated the random allocation sequence, which was done with a block randomisation of four. The Bronchiectasis Clinic's pharmacy dispensed study drugs directly to patients; therefore, allocation concealment was maintained at all times from the study investigators.

Outcomes

The primary outcome was a reduction in cough at 6 months compared with baseline, measured by the Leicester Cough Questionnaire (LCQ) score.¹⁵ We have validated use of this scoring system in bronchiectasis.¹⁶ Secondary outcomes included: forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), and the FEV₁:FVC ratio; the incremental shuttle-walk test;¹⁷ qualitative and quantitative sputum bacteriology; frequency of exacerbations; health-related quality of life, assessed by the St George's Respiratory Questionnaire (SGRQ);¹⁸ assessment of sputum neutrophil numbers and apoptosis; neutrophil activation in the airway, measured by sputum myeloperoxidase, free elastase activity, and interleukin 8 (a key neutrophil chemoattractant in bronchiectasis);¹⁹ systemic inflammation, measured by white-blood-cell count, concentrations of C-reactive protein, and the erythrocyte sedimentation rate; other markers of systemic inflammation, including amounts of interleukins 1 β , 6, 8, 10, and 12p70, and tumour necrosis factor α ; and safety of treatment.

Procedures

We did all assessments at baseline and 6 months. At 3 months, we checked LCQ scores (data presented) and blood measurements and adherence to treatment (data available on request).

We assessed cough with the LCQ. This questionnaire is a 19-item, self-completed, quality-of-life measure of chronic cough, with scores from 3 to 21 (a lower score indicates more severe cough). The minimum clinically important difference in LCQ score is 1.3 units. The LCQ is repeatable over 6 months in stable disease (intra-class correlation coefficient 0.96, 95% CI 0.93–0.97; $p < 0.0001$).¹⁶

We measured prebronchodilator FEV₁, FVC, and FEV₁:FVC by spirometry then did an incremental shuttle-walk test—an externally paced, 10 m, field-walking test

incorporating an assessment of dyspnoea before and after, with results recorded on the Borg scale (a rating of perceived exertion).¹⁷ We assessed health-related quality of life with the SGRQ.¹⁸ This questionnaire is a 50-item self-administered test with a total score ranging from 0 to 100 (a higher score indicates poorer health-related quality of life). The minimum clinically important difference in SGRQ score is 4 units.

We induced sputum with hypertonic (3%) saline for 10 min²⁰ and gathered samples for bacteriological analysis and neutrophil assessments. We determined every sample as suitable for processing if more than 25 polymorphonuclear leucocytes and fewer than ten squamous cells were present on Gram stain with low-power magnification ($\times 20$). We used 1 mL of the sputum sample for qualitative and quantitative microbiological analyses. Briefly, we homogenised sputum and liquefied it with an equal volume of dithiothreitol. To achieve dilution factors of 10^{-1} to 10^{-4} , we serially diluted the liquid samples with sterile 0.85% saline. We inoculated plates of pseudomonas isolation agar (Difco; BD Biosciences, Oxford, UK), chocolate blood agar containing bacitracin (Oxoid, Basingstoke, UK), and horse blood agar (Oxoid) with 100 μ L of each dilution and incubated plates at 37°C for 48 h. We counted colonies of pathogens to ascertain the sputum bacterial density (expressed as \log_{10} colony-forming units [cfu] per mL).

We divided the remainder of the sputum sample equally into two portions. To assess total cell numbers, we treated one part with 0.1% dithiothreitol, washed the sample twice with phosphate-buffered saline, centrifuged it at 2000 g for 10 min at 4°C, and filtered the sample once, then did cytocentrifugation at 75 g for 3 min at room temperature. We calculated cell-differential counts by counting 400 cells per sample after cytocentrifugation.²¹ We confirmed apoptosis by the colour and shape change of the neutrophil nuclei on cytopins (a method to concentrate cells) of sputum samples, as seen under the microscope (magnification $\times 1000$; figure 1). The second portion was ultracentrifuged at 750 g for 90 min at 4°C.²² The colloidal solution phase was stored at -70°C until needed for analysis of the activity of myeloperoxidase, free neutrophil elastase, and interleukin 8. We measured myeloperoxidase activity with a chromogenic substrate assay²³ and free elastase activity by spectrophotometry with a synthetic substrate (methoxysuccinyl-Ala-Ala-Pro-Val paranitroanilide; Sigma, Gillingham, UK),^{22,24} and we assayed interleukin 8 using commercially available specific ELISAs (R&D Systems, Oxford, UK).

We took 30 mL of venous blood to obtain a full-blood count; to measure the erythrocyte sedimentation rate; to ascertain amounts of C-reactive protein, urea, electrolytes, and creatine kinase; and to do liver-function tests. We centrifuged 5 mL of blood at 750 g for 10 min, collected the supernatant, and stored it at -70°C until it was needed

for measurement of amounts of proinflammatory and anti-inflammatory cytokines and chemoattractants by cytometric bead array (BD Biosciences).

We assessed patients for the presence or absence of side-effects at all study visits. If activity of alanine aminotransferase was greater than five times the normal value, or concentrations of creatine kinase were greater than three times the upper limit of normal, we stopped the assigned study treatment. We recorded all side-effects

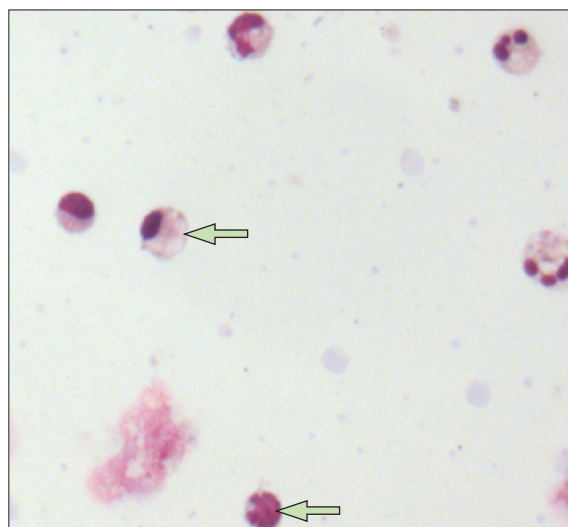


Figure 1: Neutrophil apoptosis after treatment with atorvastatin
Neutrophils (per 400 cells counted) are visualised by microscopy in a sample of sputum from a patient after 6 months of treatment with atorvastatin. Apoptotic neutrophils are indicated by arrows. Magnification $\times 1000$.

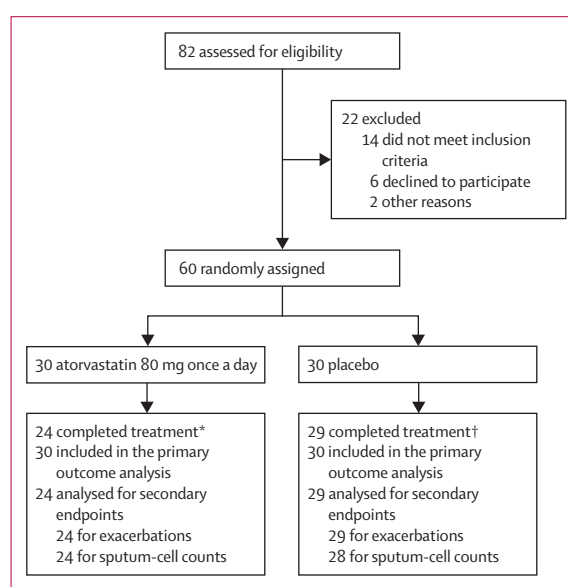


Figure 2: Trial profile

*Six patients discontinued for the following reasons: alanine aminotransferase level greater than five times the normal value (n=1); diarrhoea (n=1); headache and diarrhoea (n=2); headache (n=1); other reasons (n=1). †One patient discontinued for other reasons.

	Atorvastatin (n=30)	Placebo (n=30)
Age (years)	60.2 (10.7)	59.1 (11.4)
Women	17 (57%)	14 (47%)
Smoking status
Never	26 (87%)	18 (60%)
Former	4 (13%)	12 (40%)
Body-mass index (kg/m ²)	28.8 (8.0)	28.1 (6.3)
Body-mass index >30 kg/m ²	11 (37%)	10 (33%)
Cause of bronchiectasis
Idiopathic	21 (70%)	21 (70%)
Post infection	4 (13%)	4 (13%)
Autoimmune disease	4 (13%)	4 (13%)
Inflammatory bowel disease	1 (3%)	0
IgG ₂ deficiency	0	1 (3%)
Ischaemic heart disease	2 (7%)	1 (3%)
Asthma	19 (63%)	17 (57%)
Previous malignant disease	1 (3%)	1 (3%)
Diabetes mellitus	1 (3%)	1 (3%)
Spirometry
FEV ₁ (L)	2.1 (0.8)	2.2 (0.9)
Predicted FEV ₁ (%)	78.3 (23.8)	73.9 (24.5)
FVC (L)	3 (1.1)	3.2 (1.1)
Predicted FVC (%)	94.8 (22.8)	86.4 (25.6)
FEV ₁ :FVC (%)	69 (0.13)	69.6 (0.12)
Markers of systemic inflammation
White-cell count (× 10 ⁹ cells per L)	7.2 (2.2)	6.7 (1.9)
Neutrophils (× 10 ⁹ cells per L)	4.3 (1.9)	3.9 (1.1)
Erythrocyte sedimentation rate (mm/h)	15.1 (11.7)	14.8 (10.7)
C-reactive protein (mg/L)*	9.9 (15.5)	6.4 (7.7)
Cholesterol (mmol/L)	5.1 (1.1)	5 (0.9)
Sputum microbiology†
Potentially pathogenic microorganisms	17 (57%)	12 (40%)
Mixed normal flora	13 (43%)	17 (57%)
No sputum produced	0	1 (3%)
Other pretreatment drugs
Inhaled corticosteroids	22 (73%)	18 (60%)
Oral steroids	0	2 (7%)
Long-term antibiotic for chest (penicillin)	1 (3%)	1 (3%)
Diabetes mellitus requiring insulin	0	0
LCQ score (units)	13.1 (4.0)	15.1 (4.4)

Data are mean (SD) or number of patients (%). Data for markers of systemic inflammation are missing for three patients, and microbiological data are missing for one patient. FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. LCQ=Leicester Cough Questionnaire. *Non-SI units were used for analyses; SI units for C-reactive protein are (atorvastatin vs placebo) 0.3 (0.5) mmol/L vs 0.19 (0.2) mmol/L. †Microorganisms isolated at baseline (atorvastatin vs placebo): *Haemophilus influenzae* (8 [27%] vs 6 [20%]); *Streptococcus pneumoniae* (4 [13%] vs 1 [3%]); *Staphylococcus aureus* (3 [10%] vs 2 [7%]); other enteric Gram-negative organisms (3 [10%] vs 2 [7%]); *Pseudomonas aeruginosa* (2 [7%] vs 0); *Moraxella catarrhalis* (0 vs 1 [3%]). Some patients isolated more than one organism.

Table 1: Baseline characteristics

on a patient diary card. We defined exacerbations according to British Thoracic Society guidelines²⁵ and treated them according to baseline sputum bacteriological findings and administered 14 days of oral antibiotic treatment. We did not use macrolides because of the known interaction with statins.

Statistical analysis

We calculated the required sample size per group with a two-sided two-sample test with 5% level of significance and 90% power. We needed to detect a change of 1.3 units in the LCQ (which is the accepted minimum clinically important difference). Accounting for dropouts, we aimed to enrol 30 patients to each group.

We analysed the primary endpoint by intention-to-treat and used a modified intention-to-treat analysis for secondary endpoints. For demographic and clinical variables, we presented data as median (IQR) for continuous variables and number (%) for categorical variables, unless otherwise stated. We calculated the change from baseline to 3 months and to 6 months in the LCQ by unpaired *t* test, between patients assigned atorvastatin versus those allocated placebo (data were normally distributed). To compare the proportion of patients with either clinical improvement (measured by the LCQ) or quality-of-life gains (measured by the SGRQ), we did a binomial test and presented differences as a percentage with accompanying 95% CI. We compared categorical data between groups with the χ^2 test. We judged *p* values less than 0.05 significant. We analysed all data with SAS, version 9.2.

This study is registered with ClinicalTrials.gov, number NCT01299181.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 23, 2011, and Jan 30, 2013, 82 patients were assessed for inclusion in the study and 22 were excluded (figure 2). 60 individuals were randomised to receive treatment: 30 were assigned active treatment with high-dose atorvastatin (80 mg) and 30 were allocated placebo.

At baseline, mean LCQ scores and other variables were comparable between treatment groups (table 1). At 6 months, a significant increase (improvement) in LCQ score was seen in patients allocated atorvastatin. The mean change in LCQ score from baseline to 6 months in the atorvastatin group was 1.5 units, versus -0.7 units in the placebo group (mean difference 2.2, 95% CI 0.5–3.9; *p*=0.01; figure 3). 12 (40%) of 30 patients allocated atorvastatin had a 1.3 units or more improvement in the LCQ compared with five (17%) of 30 in the placebo group (difference 23%, 95% CI 1–45; *p*=0.04). At 3 months, the mean change in LCQ score from baseline also differed between groups, with a significant improvement noted in the atorvastatin group (mean change 2.1 units in the atorvastatin group vs -1.1 units in the placebo group; mean difference 3.3, 95% CI 0.9–5.6; *p*=0.006).

Two patients in the atorvastatin group isolated *P aeruginosa* at baseline but they were not chronically infected with the microorganism. *Haemophilus influenzae* was the most common colonising organism in both groups at baseline (table 1). At the end of treatment, 19 (63%) of 30 patients were colonised with microorganisms in the atorvastatin group (17 [57%] at baseline) versus 12 (40%) of 30 in the placebo group (12 [40%] at baseline). No significant difference in bacterial load was recorded from baseline to 6 months in each treatment group. The mean change in bacterial load after 6 months of treatment was -2.9×10^7 (SD 1.3×10^7) cfu per mL in the atorvastatin group versus 1.9×10^7 (1.2×10^7) cfu per mL in the placebo group.

24 patients in the atorvastatin group completed the study versus 29 in the placebo group. These patients were included in the modified intention-to-treat analysis of secondary endpoints (table 2). After 6 months, fewer viable neutrophils in sputum and more apoptotic neutrophils (figure 1) were counted in the atorvastatin group. In the placebo group, little change from baseline was seen. Furthermore, the median change in the number of eosinophils, basophils, or monocytes in sputum did not differ between active and placebo groups. With respect to inflammatory markers in sputum, the median change over 6 months in the amount of interleukin 8 or the activity of myeloperoxidase or free elastase was similar between the atorvastatin and placebo groups (table 2).

Baseline spirometry findings were not altered at 6 months, and no difference was noted between groups in FEV₁, FVC, or FEV₁:FVC (table 2). Exercise capacity was extended at 6 months in patients assigned atorvastatin, with a median increase of 35 m (IQR -10 to 95) compared with no escalation in distance in the placebo group.

With respect to systemic inflammation, at 6 months, the concentration of interleukin 8 in the atorvastatin group decreased from baseline amounts. However, atorvastatin had no effect on amounts of interleukins 1 β , 6, 10, or 12p70, or tumour necrosis factor α (data not shown). At 6 months, the leucocyte count, total neutrophil count, and the erythrocyte sedimentation rate were comparable with baseline levels in both the placebo and active treatment groups (table 2). However, C-reactive protein levels fell from baseline to 6 months in patients allocated atorvastatin. Independent of the C-reactive protein response, patients assigned atorvastatin had an increased LCQ score at 6 months (table 2).

Eight (33%) of 24 patients assigned atorvastatin had two or more exacerbations compared with 16 (55%) of 29 in the placebo group (relative risk ratio 0.6, 95% CI 0.3–1.2). Furthermore, five (21%) of 24 patients on atorvastatin had three or more exacerbations compared with ten (34%) of 29 in the placebo group (0.6, 0.2–1.5). A mild improvement in SGRQ scores was noted at 6 months in patients allocated atorvastatin (median

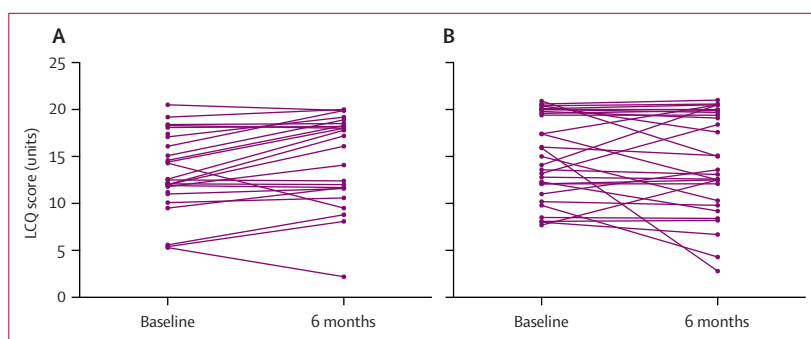


Figure 3: Reduction of cough, measured by Leicester Cough Questionnaire
LCQ=Leicester Cough Questionnaire. (A) Atorvastatin group. (B) Placebo group.

1.3 unit decrease), but this change did not meet the accepted minimum clinically important difference of a 4-unit reduction (table 2). Subscores of the SGRQ did not differ between baseline and 6 months (data not shown).

Routine blood analyses showed no significant differences between treatment groups with respect to mean changes over 6 months in urea, creatinine, alanine aminotransferase, or creatine kinase. However, the change in cholesterol from baseline to 6 months differed between groups, with patients allocated atorvastatin having a greater drop in concentration than those assigned placebo (mean difference -1.40 , 95% CI -1.77 to -1.02 ; $p < 0.0001$; table 2).

Using the change in cholesterol concentration from baseline to 6 months as an indicator of adherence to treatment, a post-hoc stratified analysis was done. In two of 29 patients assigned placebo, the amount of cholesterol fell by 1 mmol/L or more over 6 months, whereas in the atorvastatin group, 15 of 24 individuals had such a reduction. Within this subgroup of patients with a 1 mmol/L or more fall in cholesterol over 6 months, the 6-month change in LCQ score differed between treatment groups (difference 2.2, 95% CI 0.4–3.9; $p = 0.016$).

Of patients assigned atorvastatin, 26 were never-smokers and four were former smokers (table 1). All four former smokers dropped out of the study; therefore, no analysis could be done of this subgroup because of a paucity of comparative data from baseline to 6 months. Subanalyses of data for never-smokers were done in both groups; an improvement over 6 months in LCQ scores was detected in ten (38%) of 26 patients in the atorvastatin group versus two (11%) of 18 in the placebo group (1.4 units vs 0.2 units; difference 34%, 95% CI 13–57; $p = 0.04$).

Ten (33%) of 30 patients in the atorvastatin group had an adverse event compared with three (10%) of 30 in the placebo group (difference 23%, 95% CI 3–43; $p = 0.02$; table 3). No serious adverse events were reported. Two patients who were assigned atorvastatin developed leg pain in the first week of starting treatment, but this pain subsided in the second week for both individuals.

	Atorvastatin (n=24)	Placebo (n=29)
Sputum differential count (per 400 cells counted)*		
Apoptotic neutrophils	5.5 (0.0 to 15.0)	0.5 (0.0 to 3.0)
% difference of apoptotic neutrophils	15.1 (3.0)	-1.4 (0.8)
Viable neutrophils	-32.5 (-88.5 to 1.5)	-0.5 (-25 to 5)
% difference of viable neutrophils	-19.5 (5.0)	1.4 (0.6)
Basophils	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Eosinophils	0.0 (0.0 to 0.0)	0.0 (-0.5 to 1.0)
Monocytes	-1.0 (-2.5 to 1.0)	0.0 (0.0 to 2.0)
Sputum inflammatory markers*		
Interleukin 8 (pmol/L)	390 (-1487 to 1651)	399 (-479 to 1155)
Myeloperoxidase (pmol/L)	0 (-13 to 50)	0 (-32 to 86)
Neutrophil elastase (pmol/L)	0 (-980 to 280)	0 (-1588 to 553)
Spirometry		
FEV ₁ (L)	-0.01 (-0.13 to 0.13)	0.06 (-0.06 to 0.17)
FVC (L)	-0.08 (-0.30 to 0.13)	-0.07 (-0.34 to 0.20)
FEV ₁ /FVC	0.01 (-0.02 to 0.07)	0 (-0.04 to 0.07)
Exercise capacity (shuttle-walk test)		
Distance walked (m)	35 (-10 to 95)	0 (-20 to 40)
Exacerbations (n)		
0	6 (25%)	9 (31%)
1	10 (42%)	4 (14%)
2	3 (13%)	6 (21%)
≥3	5 (21%)	10 (34%)
Systemic inflammation†		
White-blood cells (×10 ⁹ cells per L)	-0.4 (-0.7 to 0.5)	-0.1 (-0.8 to 0.9)
Neutrophils (×10 ⁹ cells per L)	-0.0 (-0.4 to 0.4)	-0.1 (-0.5 to 0.9)
Lymphocytes (×10 ⁹ cells per L)	-0.1 (-0.3 to 0.1)	-0.0 (-0.2 to 0.1)
Monocytes (×10 ⁹ cells per L)	-0.0 (-0.1 to 0.1)	-0.1 (-0.1 to 0.0)
Eosinophils (×10 ⁹ cells per L)	-0.1 (-0.1 to 0.0)	-0.0 (-0.1 to 0.1)
C-reactive protein (mg/L)‡	-1.0 (-6.0 to 0.0)	0 (-3.0 to 1.0)
Erythrocyte sedimentation rate (mm/h)	-1.0 (-8.0 to 1.0)	1.0 (-4.0 to 6.0)
Interleukin 8 (pmol/L)	-2.9 (-0.6 to 28.8)	0.5 (-6.5 to 10.8)
Routine blood tests†		
Alanine aminotransferase (μkat/L)	0.03 (-0.09 to 0.09)	-0.02 (-0.09 to 0.07)
Creatine kinase (μkat/L)	-0.09 (-0.8 to 0.4)	-0.3 (-1.0 to -0.05)
Cholesterol (mmol/L)	-1.3 (-2.1 to -0.6)	0.0 (-0.2 to 0.4)
Urea (mmol/L)	0.3 (-0.9 to 1.1)	0.2 (-0.8 to 0.9)
Creatinine (mmol/L)	-1.0 (-4.0 to 3.0)	-1.0 (-4.0 to 7.0)
SGRQ score (units)	-1.3 (-4.2 to 0.0)	0.0 (-1.6 to 1.1)
LCQ score (units), analysed by C-reactive protein response†		
C-reactive protein reduction ≥1 mg/L‡	2.5 (0.1 to 3.8)	0.1 (-0.2 to 0.4)
No response, or C-reactive protein <1 mg/L‡	0.55 (-0.2 to 2.2)	-1.3 (-4.9 to 0.0)

Data are median (IQR) change from baseline to 6 months. FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. LCQ=Leicester Cough Questionnaire. SGRQ=St George's Respiratory Questionnaire. *Data missing for one patient. †Data missing for three patients. ‡1 mg/L=0.03 mmol/L.

Table 2: Secondary endpoint data

One patient in the atorvastatin group and two in the placebo group had raised creatine kinase concentrations while on treatment (less than three times the upper limit of normal), which was detected 3 months after starting treatment. Repeat measurements were taken in these patients after 1 week and the amount of creatine kinase

	Atorvastatin (n=30)	Placebo (n=30)
Leg pain	2 (7%)	0
Raised creatine kinase level*	1 (3%)	2 (7%)
Headache	3 (10%)	0
Diarrhoea	3 (10%)	0
Abdominal discomfort	1 (3%)	1 (3%)
Abnormal liver-function tests	1 (3%)	0
Haematuria	1 (3%)	0

Two patients had more than one adverse event. *Greater than two times the upper limit of normal.

Table 3: Adverse events

had either fallen or had returned to normal levels. No patients had to withdraw from the study because of high creatine kinase concentrations. In the atorvastatin group, one person developed headache while on treatment and had to withdraw from the study, and diarrhoea was reported in another patient in this group within 1 week of starting atorvastatin, leading to discontinuation because the diarrhoea persisted. A further two patients in the atorvastatin group developed both diarrhoea and headache while on treatment; both withdrew from the study because symptoms persisted. One individual in each group developed abdominal discomfort a week after starting treatment, which improved spontaneously and they did not need to stop treatment. At 3 months, one patient assigned atorvastatin had a concentration of alanine aminotransferase of 5.5 μkat/L, which was greater than five times the normal value; they were withdrawn from the study. Levels of alanine aminotransferase in this individual had returned to normal when checked 3 days after stopping treatment. One patient allocated atorvastatin developed haematuria during the first week of study treatment; however, the individual was known to have renal calculi and subsequently underwent lithotripsy for the renal calculi; study treatment continued. All patients had normal renal function throughout the study, when measured at baseline and 6 months (table 2).

Discussion

The findings of our proof-of-concept study show that high-dose atorvastatin for 6 months can significantly reduce cough (ie, increase the score on the LCQ) in patients with bronchiectasis. Our study was powered to detect a change in the LCQ of 1.3 units. The primary endpoint was achieved, confirming that our findings are robust, despite the small size of the study.

In addition to reduction of cough, markers of systemic inflammation—eg, interleukin 8 and C-reactive protein—were diminished with atorvastatin. Furthermore, the number of apoptotic airway neutrophils was amplified with a statin, whereas the total number of neutrophils in sputum fell. Exercise tolerance also increased with use of

atorvastatin. An association was noted in the atorvastatin group between reduced C-reactive protein and increased LCQ score. Also, a link was reported between statin treatment and frequency of exacerbations, with a decrease in relative risk noted in patients with two or more exacerbations. Statins had no effect on spirometric findings, airway inflammation, bacterial colonisation or load, or quality of life during the study. Subanalyses based on adherence to treatment accorded with the main study findings.

Systemic amounts of interleukin 8 fell after 6 months of atorvastatin. Interleukin 8 and leukotriene B₄ account for most of the chemotactic activity of bronchiectatic lung secretions.²⁵ However, no reduction was noted in amounts of interleukin 8 in sputum; hence, we are unable to correlate the reduction in systemic interleukin 8 to other findings in the study.

Immunomodulatory effects of statins have been studied in other chronic lung disorders. Wang and colleagues²⁶ studied patients with chronic obstructive pulmonary disease (COPD) and showed an association between previous use of a statin and fewer exacerbations needing admission. Furthermore, long-term (more than 2 years) statin use led to a 39% decrease in risk of death in individuals with COPD.²⁷ In a large study of 501 patients undergoing a lung transplant, Li and coworkers²⁸ showed strong links between postoperative statin administration and an increase in survival, maintenance of graft-lung function, and slowing of the onset of bronchiolitis obliterans.

In our study, we recorded an increase in the number and proportion of apoptotic neutrophils, a decrease in the proportion of viable neutrophils, and a reduction in the total number of neutrophils obtained from sputum of patients at the end of 6 months of atorvastatin treatment. We postulate that this fall in the overall number of neutrophils might be related to the altered lifespan of these white-blood cells in response to statin treatment. In patients with bronchiectasis, prolonged neutrophil persistence promotes excess airway inflammation.²¹ A key role exists for apoptosis—or programmed cell death—in the regulation of inflammation and the host-immune response.²⁹ Although neutrophils seem to be committed to death via apoptosis, the lifespan and functional activity of mature neutrophils can be extended substantially by proinflammatory cytokines, including granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, interferon γ , tumour necrosis factor α , and interleukin 2.²⁹ By contrast, we have shown that neutrophil apoptosis can be induced by treatment with agents such as cyclin-dependent kinase inhibitors, promoting the resolution of inflammation.^{30,31} Furthermore, in-vivo models of pneumococcal infection show that induction of apoptosis of neutrophils stimulates resolution of inflammation and accelerates recovery.³² In human cancer cell lines and murine non-cancer cells,³³ statins reduced amounts of the antiapoptotic protein

Panel: Research in context

Systematic review

We did a systematic review of PubMed, Medline, and Embase before November, 2010, with the terms: “bronchiectasis”, “COPD”, “emphysema”, “pneumonia”, “atorvastatin” or “statin”, and “randomized control trial”. We included all published reports but restricted our search to those published in English. We retrieved no positive results. To the best of our knowledge, no previous studies assessing the role of statins in bronchiectasis have been undertaken.

Interpretation

6 months of treatment with atorvastatin improved cough, assessed by the Leicester Cough Questionnaire score, in patients with bronchiectasis. The number of apoptotic neutrophils in the airways was increased with statins, suggesting a potential mechanism of action of reduction of inflammation and resolution of inflammation. We also noted a non-significant relative risk reduction for two or more exacerbations, but our proof-of-concept study was not powered to address this endpoint. Multicentre studies are needed to address whether long-term statin treatment can reduce exacerbations.

BCL2 and increased apoptosis and cell death. Statins also enhance efferocytosis (the process of removing dead cells and a key regulator of inflammation) in vitro and in vivo, which could have an important therapeutic role in diseases in which this process is impaired.³⁴

The role of statins in augmenting apoptosis of neutrophils in the airways, or the mechanism by which statins increase apoptotic neutrophils in the sputum of patients with bronchiectasis, remains to be investigated. However, the processes of switching off activated neutrophils and inducing apoptosis have therapeutic potential for bronchiectasis by promoting resolution of inflammation.

In animal models of sepsis,³⁵ statins reduced endothelial dysfunction and had antithrombotic effects that improved outcome. We recorded no adverse effects of statins on viable bacterial load in sputum.

Compared with individuals assigned placebo, fewer patients allocated atorvastatin had two or more exacerbations; this difference was not significant, but our study was not powered for this endpoint. Large multicentre studies are needed for assessment of exacerbations as the primary endpoint.

We did not see a reduction in the amounts of myeloperoxidase or free elastase in sputum, as might be expected. Apoptotic neutrophils would be expected to maintain membrane integrity until clearance and have diminished ability to degranulate, generate a respiratory burst, or undergo shape changes in response to external stimuli.³⁶ However, release of these granule contents could take place before the induction of apoptosis. Our results are similar to those of Llewellyn-Jones and

colleagues,³⁷ who gave indometacin 75 mg per day to nine patients with clinically stable bronchiectasis. Pre-treatment with indometacin led to a reduction in neutrophil chemotaxis but had no effect on sputum myeloperoxidase or free elastase activity, suggesting that these measurements in sputum might not reflect neutrophil numbers in the airways accurately. Further mechanistic studies will be needed to assess the immunomodulatory effects of statins on neutrophils.

Published work supports long-term anti-infective treatments in patients with bronchiectasis and, possibly, an anti-inflammatory approach with macrolides. Researchers on four randomised controlled trials have used a macrolide (three studies of azithromycin and one of erythromycin) as an anti-inflammatory agent in patients with bronchiectasis.^{38–41} Findings of all studies showed that use of macrolides for 6–24 months, either as a full dose or a lower maintenance dose, led to a decrease in the frequency of exacerbations in bronchiectasis. To the best of our knowledge, our study is the first to investigate the role of statins as a potential anti-inflammatory treatment in bronchiectasis (panel).

A major risk factor of long-term statin use is myositis and abnormal liver-function tests.⁴² In our study, we used the maximum dose of atorvastatin and, hence, we anticipated a high frequency of side-effects. Six patients in the atorvastatin group withdrew from the study, versus one in the placebo group; the most common cause of dropout was headache and diarrhoea. No withdrawals were attributable to myositis, but abnormal liver-function tests led to one dropout. The only withdrawal from the placebo group was for personal reasons. Thus, 24 patients assigned atorvastatin were able to tolerate the high dose (80 mg) and complete the full 6 months of treatment. Liver function needs to be tested when patients begin treatment with statins, and it should be checked after 3 months and at 1 year or earlier if any indication to do so arises. Patients should be encouraged to report symptoms of myositis, and monitoring of creatine kinase will be needed after the initial report.⁴²

One limitation of our proof-of-concept study is that the study was not powered for any of the secondary endpoints. A second limitation is that we did not undertake exact matching of active treatment and placebo tablets. However, all researchers were unaware of treatment assignments because the Bronchiectasis Clinic pharmacy dispensed the randomly allocated drugs. Furthermore, we have no reason to believe that patients were aware of their treatment assignment. Although fixed-block randomisation was used, investigators were not aware of the treatment assignment because the allocation was done by an external source (NHS Tayside). A third limitation is that some patients were former smokers, but we excluded individuals with a history of more than 15 pack-years and evidence of substantial emphysema on chest CT, making clinically significant COPD unlikely.

In conclusion, 6 months of treatment with atorvastatin improved cough in patients with bronchiectasis. The number of apoptotic neutrophils in the airways increased with atorvastatin, suggesting possible lessening of inflammation and promotion of resolution, thereby reducing cough. Although the mechanism for cough reduction is not clear, we postulate that long-term statin use will enhance apoptosis of sputum neutrophils, thereby promoting resolution of inflammation. Multi-centre studies are now needed to assess whether long-term statin treatment can reduce the frequency of exacerbations in patients with bronchiectasis. Moreover, future work should assess statin treatment in patients with severe bronchiectasis who are colonised chronically with *P aeruginosa*.

Contributors

PM implemented the study, analysed data, and wrote the report. JDC, TS, and ATH designed the study and wrote the report. CG designed the study, analysed data, and wrote the report. CH analysed data and wrote the report. MKS, CD, and JWG did microbiological analyses and wrote the report. DJD and AGR supervised experiments, interpreted data, and wrote the report. ATH was principal investigator.

Declaration of interests

We declare that we have no competing interests.

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References

- Mandal P, Hill AT. Bronchiectasis: breaking the cycle of inflammation and infection. *Lancet Respir Med* 2013; 1: e5–e6.
- Angrill J, Agusti C, de Celis R, et al. Bacterial colonisation in patients with bronchiectasis: microbiological pattern and risk factors. *Thorax* 2002; 57: 15–19.
- Cole PJ. A new look at the pathogenesis, management of persistent bronchial sepsis: a 'vicious circle' hypothesis and its logical therapeutic connotations. In: Davies RJ, ed. *Strategies for the management of chronic bacterial sepsis*. Oxford: Medicine Publishing Foundation, 1984: 1–20.
- Wilson CB, Jones PW, O'Leary CJ, et al. Systemic markers of inflammation in stable bronchiectasis. *Eur Respir J* 1998; 12: 820–24.
- Dinarello CA. Anti-inflammatory agents: present and future. *Cell* 2010; 140: 935–50.
- Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. *Nat Med* 2000; 6: 1399–402.
- Shyamsundar M, McKeown ST, O'Kane CM, et al. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. *Am J Respir Crit Care Med* 2009; 179: 1107–14.
- Fessler MB, Young SK, Jeyaseelan S, et al. A role for HMG coenzyme A reductase in pulmonary inflammation and host defense. *Am J Respir Crit Care Med* 2005; 171: 606–15.
- Chow OA, von Kockritz-Blickwede M, Bright AT, et al. Statins enhance formation of phagocyte extracellular traps. *Cell Host Microbe* 2010; 8: 445–54.
- McDowell SA, Ma Y, Kusano R, Akinbi HT. Simvastatin is protective during *Staphylococcus aureus* pneumonia. *Curr Pharm Biotechnol* 2011; 12: 1455–62.
- Boyd AR, Hinojosa CA, Rodriguez PJ, Orihuela CJ. Impact of oral simvastatin therapy on acute lung injury in mice during pneumococcal pneumonia. *BMC Microbiol* 2012; 12: 73.
- Chalmers JD, Singanayagam A, Murray MP, Hill AT. Prior statin use is associated with improved outcomes in community-acquired pneumonia. *Am J Med* 2008; 121: 1002–07.
- Davies G, Well AU, Doffman S, Watanabe S, Wilson R. The effect of *Pseudomonas aeruginosa* on pulmonary function in patients with bronchiectasis. *Eur Respir J* 2006; 28: 974–79.

- 14 Martínez-García MA, Soler-Cataluña JJ, Perpiñá-Tordera M, Román-Sánchez P, Soriano J. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. *Chest* 2007; **132**: 1565–72.
- 15 Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003; **58**: 339–343.
- 16 Murray MP, Turnbull K, MacQuarrie S, Pentland JL, Hill AT. Validation of the Leicester Cough Questionnaire in non cystic fibrosis bronchiectasis. *Eur Respir J* 2009; **34**: 125–31.
- 17 Singh SJ, Morgan MDL, Scott SC, et al. The development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992; **47**: 1019–24.
- 18 Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R. Validation of the St George's Respiratory Questionnaire in bronchiectasis. *Am J Respir Crit Care Med* 1997; **156**: 536–41.
- 19 Mikami M, Llewellyn-Jones CG, Bayley D, Hill SL, Stockley RA. The chemotactic activity of sputum from patients with bronchiectasis. *Am J Respir Crit Care Med* 1998; **157**: 723–28.
- 20 Spanevello G, Migliori GB, Sharara A, et al. Induced sputum to assess airway inflammation: a study of reproducibility. *Clin Exp Allergy* 1997; **27**: 1138–44.
- 21 Watt AP, Brown V, Courtney J, et al. Neutrophil apoptosis, proinflammatory mediators and cell counts in bronchiectasis. *Thorax* 2004; **59**: 231–36.
- 22 Hill AT, Bayley D, Stockley RA. The interrelationship of sputum inflammatory markers in patients with chronic bronchitis. *Am J Respir Crit Care Med* 1999; **160**: 893–98.
- 23 Stockley RA, Bayley DL. Validation of assays for inflammatory mediators in sputum. *Eur Respir J* 2000; **15**: 778–81.
- 24 Hill AT, Campbell EJ, Hill SL, Bayley DL, Stockley RA. Association between airway bacterial load and markers of airway inflammation in patients with stable chronic bronchitis. *Am J Med* 2000; **109**: 288–95.
- 25 Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010; **65** (suppl 1): 1–58.
- 26 Wang MT, Lo YW, Tsai CL, et al. Statin use and risk of COPD exacerbation requiring hospitalization. *Am J Med* 2013; **126**: 598–606.
- 27 Lahousse L, Loth DW, Joos GF, et al. Statins, systemic inflammation and risk of death in COPD: the Rotterdam study. *Pulm Pharmacol Ther* 2013; **26**: 212–17.
- 28 Li Y, Gottlieb J, Ma D, et al. Graft-protective effects of the HMG-CoA reductase inhibitor pravastatin after lung transplantation: a propensity score analysis with 23 years of follow-up. *Transplantation* 2011; **92**: 486–92.
- 29 Tleyjeh IM, Kashour T, Hakim FA, et al. Statins for the prevention and treatment of infections. a systematic review and meta-analysis. *Arch Intern Med* 2009; **169**: 1658–67.
- 30 Rossi AG, Sawatzky DA, Walker A, et al. Cyclin-dependent kinase inhibitors enhance the resolution of inflammation by promoting inflammatory cell apoptosis. *Nat Med* 2006; **12**: 1056–64.
- 31 Leitch AE, Lucas CD, Marwick JA, Duffin R, Haslett C, Rossi AG. Cyclin-dependent kinases 7 and 9 specifically regulate neutrophil transcription and their inhibition drives apoptosis to promote resolution of inflammation. *Cell Death Differ* 2012; **19**: 1950–61.
- 32 Koedel U, Klein M, Pfister HW. Modulation of brain injury as a target of adjunctive therapy in bacterial meningitis. *Curr Infect Dis Rep* 2010; **12**: 266–73.
- 33 Wood WG, Igbavboa U, Muller WE, Eckert GP. Statins, Bcl-2, and apoptosis: cell death or cell protection? *Mol Neurobiol* 2013; **48**: 308–14.
- 34 Merx MW, Liehn EA, Graf J, et al. Statin treatment after onset of sepsis in a murine model improves survival. *Circulation* 2005; **112**: 117–24.
- 35 Morimoto K, Janssen WJ, Fessler MB, et al. Lovastatin enhances clearance of apoptotic cells (efferocytosis) with implications for chronic obstructive pulmonary disease. *J Immunol* 2006; **176**: 7657–65.
- 36 Houck JC. Chemical messengers of the inflammatory process. Oxford: Elsevier/North-Holland Biomedical Press, 1979.
- 37 Llewellyn-Jones CG, Johnson MM, Mitchell JL, et al. In vivo study of indomethacin in bronchiectasis: effect on neutrophil function and lung secretion. *Eur Respir J* 1995; **8**: 1479–87.
- 38 Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012; **380**: 660–67.
- 39 Serisier DJ, Martin ML, McGuckin MA, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *JAMA* 2013; **309**: 1260–67.
- 40 Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA* 2013; **309**: 1251–59.
- 41 Valery PC, Morris PS, Byrnes CA, et al. Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. *Lancet Respir Med* 2013; **1**: 610–20.
- 42 Joint Formulary Committee. British National Formulary number 67: chapter 2, cardiovascular system—section 2.12, lipid-lowering drugs; statins. London: BMJ Publishing Group and Royal Pharmaceutical Society, 2014.